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AUTHOR(S):

Inoue, Yoshihiko; Tanimoto, Shigeo; Nakamura, Kaoru; Ohno, Atsuyoshi

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## Asymmetric Reduction of Methyl Ketones Having a 1,3-Dithiolane or 1,3-Dithiane Moiety by Bakers' Yeast

Yoshihiko INOUE,\* Shigeo TANIMOTO,\* Kaoru NAKAMURA,\*\* and Atsuyoshi OHNO\*\*

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4-(2-Methyl-1,3-dithiolan-2-yl)-2-butanone (**1a**), 4-(2-methyl-1,3-dithian-2-yl)-2-butanone (**1b**), and 5-(1,3-dithian-2-yl)-2-pentanone (**1c**) were reduced with bakers' yeast to the corresponding hydroxy compounds. The enantioselectivity in the reduction of **1b** was superior to that of the corresponding dithiolane derivative (**1a**). Several efforts to increase the enantioselectivities of the reduction were attempted.

**KEY WORDS:** 4-(2-Methyl-1,3-dithiolan-2-yl)-2-butanone/ 4-(2-Methyl-1,3-dithian-2-yl)-2-butanone/ 5-(1,3-Dithian-2-yl)-2-pentanone/ Bakers' yeast/ Enantioselectivity/

The application of biocatalysis in selective transformations of synthetic substrates is a useful method to provide chiral building blocks for synthesis.<sup>1)</sup> A microorganism may be simply viewed by organic chemists as a collection of enzymes with all necessary co-factors for catalysis. Among microbes, bakers' yeast is the most frequently used microorganism for preparing optically active alcohols mainly because bakers' yeast is commercially available in quantity and the reaction using it is easy to carry out.<sup>2)</sup> The optically active alcohols in which a sulfur containing group is attached are useful chiral building blocks because of the easiness of transformations of the group to the other functional groups. Thus, many chiral natural products have been synthesized from such the optically active alcohols.<sup>3)</sup> In this report, we will describe the asymmetric reduction of methyl ketones having a 1,3-dithiolane or 1,3-dithiane moiety by bakers' yeast.

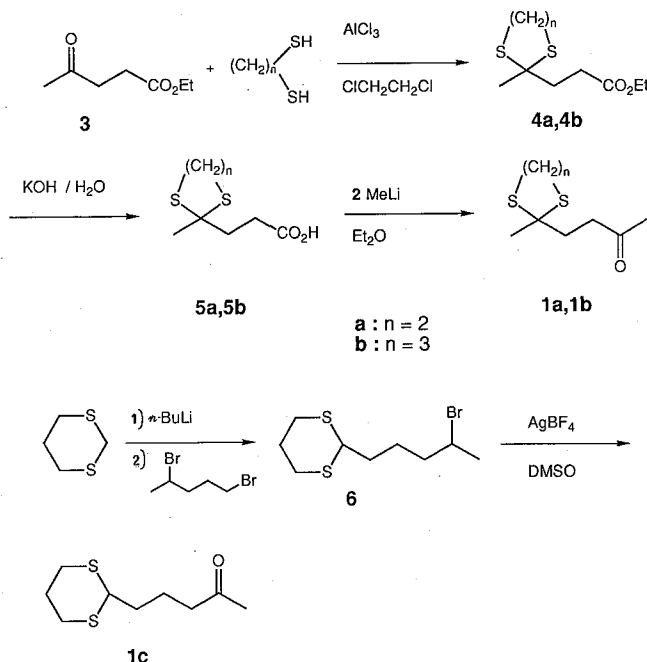
### RESULTS AND DISCUSSION

The starting substrates, 4-(2-methyl-1,3-dithiolan-2-yl)-2-butanone (**1a**), and 4-(2-methyl-1,3-dithian-2-yl)-2-butanone (**1b**) were prepared both from ethyl 4-oxopentanoate. Dithioacetalization with 1,2-ethanedithiol or 1,3-propanedithiol in the presence of aluminum(III) chloride in 1,2-dichloroethane followed by hydrolysis with aqueous potassium hydroxide gave 3-(2-methyl-1,3-dithiolan-2-yl)propanoic acid (**5a**) or 3-(2-methyl-1,3-dithian-2-yl)propanoic acid (**5b**), respectively. The reaction of **5** with two equivalents of methyl-lithium in ether afforded the corresponding methyl ketones (**1a,b**). The third substrate, 5-(1,3-dithian-2-yl)-2-pentanone (**1c**) was prepared from dithiane and 1,4-dibromopentane.

\* 井上欣彦, 谷本重夫: Laboratory of Petroleum Chemistry, Institute for Chemical Research, Kyoto University, Uji, Kyoto 611.

\*\* 中村薫, 大野惇吉: Laboratory of Organic Unit Reaction, Institute for Chemical Research, Kyoto University, Uji, Kyoto 611.

# Asymmetric Reduction of Ketones Having a Dithioacetal Moiety by Bakers' Yeast

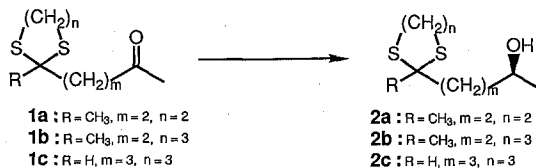


The reaction of 1,3-dithian-2-yl anion with 1,4-dibromopentane afforded 5-(1,3-dithian-2-yl)-2-bromopentane (**6**). Oxidation of **6** with silver tetrafluoroborate in dimethyl sulfoxide (DMSO) gave **1c**. Details are described in the experimental section.

Three methyl ketones containing a cyclic dithioacetal moiety (**1a-c**) were reduced with bakers' yeast. These compounds were reduced into the corresponding alcohols of *S*-configuration<sup>4)</sup> as was anticipated from the well known Prelog's rule<sup>5)</sup> which indicates the production of *S*-alcohol in microbial reductions. Usually, bakers' yeast reduction of  $\beta$ -keto esters proceeds smoothly. For example, 20 mmol of ethyl 3-oxobutanoate is reduced with 14 g of bakers' yeast in 95% yield within 4 h. On the contrary, the reduction of methyl ketones having a 1,3-dithiolane or 1,3-dithiane moiety required larger amounts of bakers' yeast as well as longer reaction times. The results are listed in Table 1.

The absolute configurations of the obtained products were determined to be *S* by the comparison of the sign of optical rotation with that of (*S*)-1-(1,3-dithian-2-yl)-2-propanol ( $[\alpha]_{\text{D}}^{20} = +24.7^\circ$  (c, 2.0, chloroform)).<sup>7)</sup> The e.e.s of the products were determined by <sup>1</sup>H NMR spectroscopy. Thus, the obtained products were converted to the corresponding MTPA derivatives. The relative intensities of <sup>1</sup>H NMR spectra of the methyl, methine, or methoxy group included in the derivatives were employed for e.e. determination.

As can be seen from Table 1, the reduction of **1a** afforded the corresponding hydroxy compound (**2a**) with moderate chemical yields (11–32%). The reaction at elevated temperature (40°C) gave a relatively high enantiomeric excess (e.e.), while the chemical yield decreased compared to that from the reduction at room temperature (25°C). On increasing the amount of bakers' yeast, the e.e. of the obtained alcohol was increased. The maximum e.e. (86%) was obtained when 2 mmol of **1a** was reduced with 100 g of bakers'

Table 1. Reduction of **1** by Bakers' Yeast

Substrate <sup>a)</sup> (Conc./M)	Bakers' yeast/g	Glucose/g	Reaction time/day	Yield/%	e.e./%	[α] <sub>D</sub> <sup>25/°</sup> (c, CHCl <sub>3</sub> )	Recov. 1/%
<b>1a</b> (0.02)	10.0	2.0	7	27	24	+0.72 (2.52)	64
<b>1a</b> (0.02) <sup>b)</sup>	30.0	6.0	8	11	70	+6.30 (1.01)	69
<b>1a</b> (0.02)	50.0	5.0	14	32	34	+2.00 (2.26)	10
<b>1a</b> (0.002)	100.0	50.0	7	17	86	+2.30 (1.59)	45
<b>1b</b> (0.02)	10.0	2.0	7	13	90	+7.24 (2.61)	67
<b>1b</b> (0.02)	30.0	6.0	7	9	68	+6.89 (1.61)	60
<b>1b</b> (0.02) <sup>c)</sup>	30.0	6.0	7	20	69	+3.20 (3.78)	53
<b>1b</b> (0.02) <sup>d)</sup>	30.0	6.0	7	15	35	+5.75 (2.61)	66
<b>1c</b> (0.01) <sup>e)</sup>	34.6	3.5	6	97	38	+1.20 (3.45)	0
<b>1c</b> (0.01) <sup>f)</sup>	49.0	0	7	45	4	-0.30 (2.12)	0
<b>1c</b> (0.01) <sup>f,g)</sup>	49.0	0	7	53	21	-1.50 (5.02)	0

<sup>a)</sup> The reaction was carried out using 2 mmol of the substrate at room temperature unless otherwise indicated.

<sup>b)</sup> Reaction temperature was 40°C.

<sup>c)</sup> Conducted under a nitrogen atmosphere.

<sup>d)</sup> The reaction was carried out under irradiation with 60 W tungsten lamp.

<sup>e)</sup> The amount of substrate was 0.69 mmol.

<sup>f)</sup> The amount of substrate was 0.98 mmol.

<sup>g)</sup> Allyl alcohol (1.96 mmol) was added.

yeast. The reduction of **1b** afforded the alcohol **2b** with higher e.e.s than those of **2a**. Contrary to the reduction of **1a**, increasing the amount of bakers' yeast decreased the e.e. of **2b**, for example, from 90% at 10 g bakers' yeast to 68% at 30 g bakers' yeast (per 2 mmol of **1b**). Irradiation by a tungsten lamp markedly decreased the e.e. The reduction of **1c** afforded the highest chemical yield with the lowest enantioselectivity among the reactions of three substrates used in this study. The relative high reactivity of **1c** compared to **1a** or **1b** is due to the length of carbon chain between the carbonyl group and the sterically large cyclic dithioacetal moiety. The low enantioselectivity of the reduction of **1c** suggests this idea.

## EXPERIMENTAL

**Instruments.** <sup>1</sup>H NMR spectra were recorded on a Varian VXR-200 (200 MHz) and a JEOL GX-400 (400 MHz) spectrometer in CDCl<sub>3</sub> with (CH<sub>3</sub>)<sub>4</sub>Si as an internal reference. Optical rotations were measured with a Perkin-Elmer 241 polarimeter.

**Materials.** Organic reagents were purchased from Nakarai Tesque Co. and Aldrich Chemical Co. unless otherwise indicated. Solvents and commercially available starting materials were generally used without additional purification unless otherwise indicated.

Pyridine and benzene were refluxed on calcium hydride for 1 day and distilled before the use. Pressed "raw" and dry bakers' yeast were purchased from Oriental Yeast Co. and they were stored in a refrigerator. "Raw" yeast was used within 1 week after it had been purchased because the activity in the reduction decreased on storage for longer time. Dry yeast could be stored more than 1 month without decreasing its activity.

**Ethyl 3-(2-Methyl-1,3-dithiolan-2-yl)propanoate (4a).** A stirred solution of ethyl 4-oxopentanoate (13.6 g, 94.7 mmol) and 1,2-ethanedithiol (7.94 ml, 94.7 mmol) in 1,2-dichloroethane (100 ml) was cooled to 0°C and aluminum(III) chloride (12.6 g, 94.7 mmol) was added slowly to the solution. The resulting mixture was stirred at room temperature for 1 day. Water (100 ml) was added to the mixture and the organic layer was separated. The aqueous layer was extracted with dichloromethane (100 ml  $\times$  3). Combined organic layer was washed three times with 100 ml of aqueous sodium bicarbonate and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* and the residue was distilled, yielding 16.6 g (75.4 mmol, 79.6%) of ethyl 3-(2-methyl-1,3-dithiolan-2-yl)propanoate (**4a**), bp 92–102°C (2.2 mmHg).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.23 (t, 3H,  $J = 2.1$  Hz), 1.76 (s, 3H), 2.15–2.28 (m, 2H), 2.50–2.64 (m, 2H), 3.18–3.42 (m, 4H), 4.11 (q, 2H,  $J = 2.2$  Hz).

**3-(2-Methyl-1,3-dithiolan-2-yl)propanoic Acid (5a).** A mixture of **4a** (11.5 g, 52.3 mmol) and 105 ml of 1M aqueous potassium hydroxide solution was stirred at room temperature for 1 day. The resulting solution was acidified with 2N HCl (100 ml) and extracted with ether (100 ml  $\times$  3). The combined ethereal solution was washed with water (100 ml  $\times$  3) and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* and the residue was chromatographed on a silica gel column. Elution of the column with dichloromethane yielded 9.63 g (50.1 mmol, 95.7%) of **5a**.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.78 (s, 3H), 2.17–2.32 (m, 2H), 2.54–2.75 (m, 2H), 3.19–3.49 (m, 4H).

**4-(2-Methyl-1,3-dithiolan-2-yl)-2-butanone (1a).** A stirred ethereal solution (25 ml) of **5a** (5.17 g, 26.9 mmol) was cooled with ice bath, and methyllithium (54.9 ml of 0.98 M ethereal solution, 53.8 mmol) was added dropwise to the solution under nitrogen. The resulting mixture was stirred at room temperature for 7 h. After the mixture was cooled to 0°C, a saturated aqueous ammonium chloride solution (50 ml) was added slowly. The resulting mixture was extracted with ether (50 ml  $\times$  3) and the combined ethereal solution was dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* and the residue was chromatographed on a silica gel column. Elution of the column with ether-hexane (1 : 5) yielded 2.52 g (13.3 mmol, 49.3%) of **1a**.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.76 (s, 3H), 2.17 (s, 3H), 2.11–2.28 (m, 2H), 2.63–2.80 (m, 2H), 3.20–3.39 (m, 4H).

**Ethyl 3-(2-Methyl-1,3-dithian-2-yl)propanoate (4b).** A stirred solution of ethyl 4-oxopentanoate (28.8 g, 200 mmol) and 1,3-propanedithiol (20 ml, 200 mmol) in 1,2-dichloroethane (200 ml) was cooled to 0°C and aluminum(III) chloride (26.6 g, 200 mmol) was added slowly to the solution. The resulting mixture was stirred at room temperature for 2 days. Water (200 ml) was added to the mixture and the organic layer was separated. The aqueous layer was extracted with dichloromethane (200 ml  $\times$  3). Combined organic layer was washed with aqueous sodium bicarbonate (100 ml  $\times$  3) and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* and the residue was distilled, yielding 20.6 g (88.0 mmol, 44.0%) of ethyl 3-(2-methyl-1,3-dithian-2-yl)propanoate (**4b**), bp 97.5–106.5°C (1.8 mmHg).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.25 (t, 3H,  $J = 2.1$  Hz), 1.51 (s, 3H), 1.75–

2.10 (m, 2H), 2.23–2.37 (m, 2H), 2.37–2.57 (m, 2H), 2.60–3.03 (m, 4H), 4.12 (q, 2H,  $J = 2.1$  Hz).

**3-(2-Methyl-1,3-dithian-2-yl)propanoic Acid (5b).** A mixture of **4b** (20.6 g, 88.0 mmol) and 176 ml of 1 M aqueous potassium hydroxide solution was stirred at room temperature for 1 day. The resulting solution was acidified with 2 N HCl (180 ml) and extracted with ether (100 ml  $\times$  3). The combined ethereal solution was washed with water (100 ml  $\times$  3) and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* and the residue was chromatographed on a silica gel column. Elution of the column with dichloromethane yielded 16.93 g (82.1 mmol, 93.3%) of **5b**.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.53 (s, 3H), 1.75–2.13 (m, 2H), 2.23–2.42 (m, 2H), 2.49–2.66 (m, 2H), 2.66–2.85 (m, 2H), 2.85–3.05 (m, 2H).

**4-(2-Methyl-1,3-dithian-2-yl)-2-butanone (1b).** A stirred ethereal solution (25 ml) of **5b** (5.00 g, 24.2 mmol) was cooled with ice bath and methyllithium (34.6 ml of 1.4 M ethereal solution, 48.5 mmol) was added dropwise to the solution under nitrogen. The resulting mixture was stirred at room temperature for 19 h. After the mixture was cooled to 0°C, a saturated aqueous ammonium chloride solution (50 ml) was added slowly. The resulting mixture was extracted with ether (50 ml  $\times$  3) and the combined ethereal solution was dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* and the residue was chromatographed on a silica gel column. Elution of the column with ether-hexane (1 : 4) yielded 2.07 g (10.2 mmol, 41.9%) of **1b**.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.51 (s, 3H), 1.73–2.09 (m, 2H), 2.17 (s, 3H), 2.13–2.29 (m, 2H), 2.53–2.98 (m, 6H).

**5-(1,3-Dithian-2-yl)-2-bromopentane (6).** A hexane solution of butyllithium (1.6 M, 15.6 ml, 25 mmol) was added dropwise to a cooled (–78°C) solution of 1,3-dithiane (3.00 g, 25.0 mmol) in tetrahydrofuran (50 ml) under a nitrogen atmosphere. The resulting mixture was stirred for 30 min at the same temperature and then for 30 min at 0°C. After the reaction mixture was cooled to –78°C, 1,4-dibromopentane (3.40 ml, 25.0 mmol) was added dropwise. The resulting mixture was stirred for 30 min at –78°C and then for 2 days at room temperature. After the mixture was cooled to 0°C, a saturated aqueous solution of ammonium chloride (50 ml) was added and the mixture was extracted with ether (50 ml  $\times$  3). The combined ethereal solution was dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* and the residue was chromatographed on a silica gel column. Elution of the column with hexane yielded 6.19 g (24.5 mmol, 97.2%) of **6**.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.44–2.21 (m, 11H), 2.70–3.00 (m, 4H), 3.90–4.20 (m, 2H).

**5-(1,3-Dithian-2-yl)-2-pentanone (1c).** A DMSO solution (3.6 ml) of silver tetrafluoroborate (0.702 g, 3.60 mmol) was added slowly to a solution of **6** (0.765 g, 3.00 mmol) in DMSO (1.2 ml) at room temperature. After the resulting mixture was stirred for 18 h at the same temperature, triethylamine (0.48 ml) was added and the mixture was stirred for 15 min. The mixture was extracted with ether (10 ml  $\times$  3) and the combined ethereal extract was dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* and the residue was chromatographed on a silica gel column. Elution of the column with ether-hexane (1 : 4) yielded 0.141 g (0.691 mmol, 23.0%) of **1c**.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.52–1.86 (m, 4H), 1.92–2.11 (m, 2H), 2.04 (s, 3H), 2.37 (t, 2H,  $J = 2.0$  Hz), 2.66–2.82 (m, 4H), 3.93 (t, 1H,  $J = 1.9$  Hz).

**Reduction of 1 with Bakers' Yeast (General Procedure).** Glucose and one of **1** were

added to a suspension of bakers' yeast in water and the whole suspension was stirred for indicated period at room temperature. Then, ethyl acetate and celite (Hyflo Super-Cell) were added to the reaction mixture and it was filtered. The filtrate was extracted with ethyl acetate. Bakers' yeast was washed with ethyl acetate and the combined organic portion was washed with water, dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was subjected to a column chromatography on silica gel (eluent: dichloromethane) giving the reduced product. The chemical yields, e.e.s, and the reaction conditions are listed in Table 1.

**Determination of the e.e.s of 2.** The e.e.s of the products were determined by  $^1\text{H}$  NMR analyses of the corresponding MTPA derivatives. The e.e. of **2a** was determined from the relative intensities of one methyl group at 1.29 (*R*) and 1.37 (*S*) or another methyl group at 1.66 (*R*) and 1.73 (*S*) of the MTPA derivative of **2a**. The e.e. of **2b** was determined from the relative intensities of one methyl group at 1.54 (*R*) and 1.46 (*S*) or the methoxy group at 3.58 (*R*) and 3.54 (*S*) of the MTPA derivative of **2b**. The e.e. of **2c** was determined from the relative intensities of the methine group, which is included in the 1,3-dithian ring, at 4.03 (*R*) and 3.93 (*S*) of the MTPA derivative of **2c**.

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